

Date: April 23, 2004

United States Patent & Trademark Office
Assistant Commissioner for Patents
Dr. Samuel Wei Liu, Ph.D., Examiner
Group Art Unit: 1653
P.O. Box 1450
Alexandra, VA 22313-1450

Dear Dr. Liu:

Enclosed is my response to the Office Action dated on 02/26/2004, concerning the application of 10/004,176.

A. Obviousness is evaluated according to Granham v John Deere Co. by reviewing four factors:

1. Determining the scope and contents of the prior art;
2. Ascertaining the differences between the prior art and the claims in issue;
3. Resolving the level of ordinary skill in the pertinent art; and
4. Evaluating evidence of secondary considerations

Ruoslahti E. et al. (US Pat. No. 5654270) indicates the use of pharmaceutical composition comprising decorin for wounds, in particular, for dermal wounds, resulting from burns, injuries or cosmetic surgery. A wound or dermal wound refers to an injury to the body (as from violence, accident, or surgery) that involves laceration or breaking of a membrane (as the skin) and usually damage to underlying tissue. However, the current application teaches to apply a cosmetic composition comprising decorin to a normal skin. Normal skin has an intact membrane, non-injury, non-laceration, and serves many functions crucial to survival and health, such as protection against the elements and thermoregulation. Dermal wound does not have the same functions as the normal skin does. It is obvious that wound or dermal wound and normal skin are two totally different anatomic or pathological areas. Therefore, the current invention was not *prima facie* obvious to make and use the invention at the time it was made.

Normal skin is a relatively impermeable protective barrier to the outward loss of body fluids and the inward penetration of various substances and microorganisms. Dermal wound is an injury, opened, and defected skin, with the protective barrier broken. It is obvious that many substances that are normally impermeable to the skin can easily get through the wound area into the deeper layer of the skin. Therefore, the current invention is different to the prior art.

Ruoslahti E. et al. (US Pat. No. 5654270) indicates the use of pharmaceutical composition comprising decorin for wounds, in particular, for dermal wounds, resulting from burns, injuries or cosmetic surgery to reduce dermal scarring. Dermal scarring due

to dermal wound is a series of healing process involving three phases: substrate, proliferation, and remodeling. The proliferative phase (10 to 14 days after wounding) results in regeneration of epidermis, neoangiogenesis, and proliferation of fibroblasts with increased collagen synthesis and closure of the skin defect. In the final remodeling phase that takes place over 6 to 12 months after wounding, a more stable form of collagen is laid down to form a scar. Sometimes, too much collagen is deposited in the healing wound to create an elevated hypertrophic scar (red, raised scar within the boundaries of the original wound) or keloid (scar tissue extending beyond the boundaries of original injury into surrounding normal tissue). By definition of the formation of a scar, reducing scarring in the wounds (e.g. cosmetic surgery) implies to reduce the formation of collagen fibers in the wound. However, the current application teaches to use a cosmetic composition comprising decorin for the normal skin to reduce skin aging, i.e. wrinkles of skin. Skin aging is a complex biological phenomenon involving in a genetically determined degenerative aging process. It is obvious that dermal scarring due to dermal wound and skin aging due to senescence are two distinct natural processes. Therefore, the current invention was not *prima facie* obvious to make and use the invention at the time it was made.

Although reducing scarring and reducing skin aging, i.e. wrinkle of the skin, service a similar cosmetic purpose to make a better appearance, they are two entirely different approaches. Reducing the formation of collagen in the wound is to reduce scarring. In contrast, reducing skin aging, i.e. wrinkle of skin, is involved in stimulating the synthesis of collagen or protecting the skin collagen. There are many skin disorders including a scar from cosmetic surgery and there are many different, distinct, and unique approaches to treat them with a similar cosmetic purpose. Use of pharmaceutical composition comprising decorin to reduce scarring according to Ruoslahti E. et al. (US Pat. No. 5654270) is only one of many cosmetic approaches. It is not obvious that decorin reducing scarring can reduce skin aging, because they are two different and opposite processes. Therefore, the current invention is a different one from the prior art.

Ruoslahti E. et al. (US Pat. No. 5654270) indicates the use of pharmaceutical composition comprising decorin for wound or dermal wound, a defect skin or opened skin or injured skin, but fails to demonstrate that decorin can penetrate through a normal intact skin. Decorin has a molecular weight 40,000 Dalton. Normal skin is impermeable even for low molecular weight (>500 Dalton) agents due to the excellent barrier of the stratum corneum. In the current invention, decorin in the deformable lipidvesicle delivery system is applied to a normal intact skin and unexpectedly reduces the skin aging, i.e. wrinkle of the skin. Deformable lipidvesicles that can easily penetrate through the surface skin to underlying layers have been used cosmetically or dermatologically to deliver large active anti-aging molecules into the skin (Weiner et al., *J. Drug Target.* 2:405, 1994; Cevc, G. *Crit. Rev. Ther. Drug Carrier Syst.* 13:257, 1996; Perugini et al., *Int. J. Pharm.* 196:51, 2000; Fiume, Z. *Int. J. Toxicol.* 20 Suppl 1:21, 2001)

The statement of your DETAILED ACTION in page 4 “This application currently names joint inventors” is an error. Please see the attachment of the copy of the DECLARATION to confirm that this application does not name joint inventors.

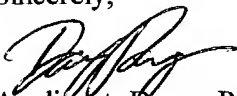
B. In the claims:

The application is amended as follows:

1. A cosmetic or pharmaceutical or dermatological composition containing an effective amount of decorin dissolved for topical administration in a cosmetically or dermatologically acceptable vehicle.
2. The composition of claim 1, wherein said decorin is obtained from nature without modification or produced by recombinant means.
3. The composition of claim 2, wherein said decorin comprises the mature core protein set forth as amino acids 1-329 of SEQ ID NO:6.
4. The composition of claim 3, wherein said decorin core protein is present in an amount between 0.5 microgram/ml and 5,000 microgram/ml.
5. The composition of claim 4, wherein said decorin is present in an amount between 5 microgram/ml and 500 microgram/ml.
6. A method of treating the skin of a human to reduce signs of skin aging (e.g. lines, wrinkles, loss of elasticity, sagging, skin dryness and unevenness, blotches, age spots, pigmented spots), comprising applying to the skin a cosmetic or dermatological composition containing an effective amount of decorin dissolved in a cosmetically or dermatologically acceptable vehicle.
7. The method of claim 6 wherein the composition comprise decorin obtained from nature without modification or produced by recombinant means.
8. The method of claim 7 wherein the composition comprise the decorin core protein set forth as amino acids 1-329 of SEQ ID NO:6.
9. The method of claim 8 wherein the composition comprises decorin in an amount from 0.5 microgram to 5,000 microgram/ml.
10. The method of claim 9 wherein the composition comprises decorin in an amount from 5 microgram/ml to 500 microgram/ml.

C. A copy of the Office Action Summary.

Sincerely,


Applicant: Danny Pang